IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of Baumann *et al.*	:	Group Art Unit: 1623 Examiner Eric Olson
Serial No.: 10/627,944	:	
Filed: July 28, 2003	:	
For: Method for Treating Damaged Skin	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1.132 Affidavit of Neil A. Swanson, M.D.

I, Neil A. Swanson, M.D., being duly sworn, depose and say:

1. I have prepared this Affidavit so that it may be considered by the US Patent and Trademark Office in connection with the examination of US Patent Application Serial No. 10/627,944 entitled "Method for Treating Damaged Skin."

2. I am Chairman of the Department of Dermatology and Professor of Dermatology, Otolaryngology and Surgery at Oregon Health & Science University ("OHSU"). I also serve as President of the OHSU Medical Group and as the Associate Dean for Clinical Affairs for the OHSU School of Medicine. Prior to joining OHSU to serve as director of dermatologic surgery, I was the director of the surgical unit and multidisciplinary melanoma program at the University of Michigan.

3. I received my Doctor of Medicine in 1976 from the University of Rochester School of Medicine. In 1979, I completed a Dermatology Residency and Mohs Chemosurgery Fellowship, both at the University of Michigan Medical School. In 1980, I completed an Advanced Dermatologic Surgery Fellowship at the University of California, San Francisco.

4. I serve on the Board of Directors of the American Dermatology Association and am the past president of the American Society of Dematologic Surgery. I have authored more than a hundred journal articles, authored or edited five textbooks and contributed chapters to numerous textbooks. I lecture internationally on the detection and treatment of skin cancer as well as cosmetic surgery procédures.

5. In preparing this Affidavit, I have reviewed the following two publications: Stockfleth *et al.*, "Successful treatment of actinic keratosis with imiquimod cream 5%: a report of six cases," *Br. J. Dermatol.*, Vol. 144, pp. 1050 – 1053 (2001) and US Patent Application Publication No. 2003/0072724 (to Maibach *et al.*)

6. Topically-applied imiquimod (5%) has been approved by the FDA for the treatment of three dermatologic conditions: (i) clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults; (ii) biopsy-confirmed, primary superficial basal cell carcinoma in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), when surgical methods are medically less appropriate and patient follow-up can be reasonably assured; and (iii) external

genital and perianal warts in patients 12 years and older. The first two indications were approved in March 2004 and July 2004, respectively.

7. Stockfleth *et al.* (2001) define actinic keratoses (AKs) as "epidermal tumours which result from the proliferation of transformed neoplastic keratinocytes." The Stockfleth article continues to explain that AKs can progress into thickened or hypertrophic lesions, which can subsequently develop into squamous cell carcinomas. AKs are, therefore, sometimes referred to as "precancerous lesions."

8. Clinically, AKs present as easily palpable, rough or "gritty," usually erythematous patches, ranging in size from several millimeters up to about one centimeter in diameter. Histologically, AKs are basophilic and variable in shape and size, with large, polymorphic and heterochromatic nuclei. (The latter is sometimes referred to as "nuclear atypia.") AKs are also characterized by dysplasia and loss of cellular polarity. Except in their hypertrophic form, AKs show little or no cellular infiltration.[1]

9. Normal (*i.e.*, non-precancerous) photodamaged skin and aged skin differ considerably from AKs, both in clinical and histological presentation.

10. Aged skin results from both intrinsic and extrinsic factors. Intrinsic aging is manifested as fine lines and deepening of facial expression lines. Intrinsically-aged skin is thin and inelastic. Extrinsic aging can cause aged skin to appear yellowed and blemished and have mottled pigmentation, coarse wrinkles and

[1] D Elder *et al.* (eds.), *Lever's Histopathology of the Skin,* p. 702 (8th ed., 1997); B. Gilchrest, *Photodamage*, p. 169 (1995).

furrowing. On physical examination, extrinsically-aged skin is thickened, lax, rough and leathery.

11. Histologically, aged skin shows varying degrees of cytological atypia (both of keratinocytes and melanocytes). On microscopic examination, normal, photodamaged skin exhibits elastosis – thickened, twisted degraded elastic fibers which, over time, degenerate into an amorphous mass. The histology of normal photodamaged skin is also characterized by a decrease in the quantity of collagen fibers and the presence of inflammatory infiltrate. Intrinsically-aged skin is characterized histologically by a flattening of rete pegs at the dermoepidermal junction.[2]

12. The invention by Drs. Baumann and Welsh does not relate to the treatment of precancerous skin conditions. One aspect of the invention by Drs. Baumann and Welsh relates to treating intrinsically-aged skin, which they describe as skin containing fine lines or wrinkles. Another aspect of the invention by Drs. Baumann and Welsh relates to the treatment of normal photodamaged skin, which they define in Paragraph [0021] to mean "non-precancerous skin."

13. In summary, AK differs considerably – both in clinical presentation and histological analysis – from aged skin and normal, photodamaged skin. The 2001 Stockfleth article is focused on the use of imiquimod in clinically-diagnosed cases of AK. It does not teach or suggest the use of imiquimod in either intrinsically-aged skin or normal, photodamaged skin.

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[2] ZD Draelos, "Topical Treatments for Benign Photodamage" in DJ Goldberg (ed.), *Photo-damaged Skin*, pp.146 – 147 (2004).

14. Drs. Baumann and Welsh teach daily administration of imiquimod for treating normal photodamaged skin and aged skin. In the 2001 Stockfleth article, as well as a follow-up publication, Stockfleth *et al.* caution that use of imiquimod at 5% caused significant irritation, necessitating a decrease in the frequency of application to at most twice per week.[3] These adverse effects would be taken into account by a cosmetic dermatologist and would have taught him/her not to treat non-cancerous or non-viral skin conditions in the manner described by Drs. Baumann and Welsh.

15. In the Maibach *et al.* patent application, the sole reference to imiquimod is with respect to the treatment of warts in Paragraph [0092]. Warts are caused by the papilloma virus. The invention by Drs. Baumann and Welsh specifically disclaims the use of imiquimod in patients being treated for viral infection.

16. The Maibach application does not discuss or suggest the use of imiquimod to treat intrinsically-aged skin as described above. Instead, Maibach *et al.* teach the use of known depigmenting active ingredients – hydroquinone, kojic acid, glycolic acid and other alpha-hydroxy acids, and artocarpin – for the treatment of hyperpigmentation in a specific dermopharmaceutical base containing specific permeation enhancers. *See*, *e.g.*, Paragraph [0095].

17. I am familiar with the literature and research regarding new uses of imiquimod. For example, I have read a 2005 review article by Vender entitled "Innovative Uses of Imiquimod", which reports on the successful treatment of

[3] JM Spencer, "Actinic Keratoses and Atypical Nevi", in Goldberg (ed.), *Photodamaged Skin*, p. 8 (2004) citing Stockfleth *et al.*, "A randomized double blind, vehicle controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses" *Arch. Dermatol.*, Vol. 138, No.11, pp. 1498-1502 (2002).

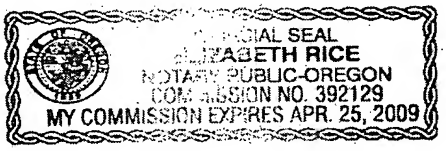
over forty dermatologic conditions, anecdotally or in clinical trial settings. *Journal of Drugs in Dermatology*, Vol. 4, No. 1, pp. 58 – 63. The Vender article is an extensive review of clinical trials, case reports and letters published in peer-reviewed journals regarding imiquimod use in treating skin disorders. It is based on searches of five medical/scientific databases – MEDLINE, EMBASE, Biosis, SciSearch and International Pharmaceutical Abstracts. Treatment of normal photodamaged skin (i.e., non-precancerous skin) is not mentioned. Nor is treatment of fine lines and wrinkles in aged skin.

18. In March 2006, Drs. Albert Kligman and Raymond Cornelison, Jr. presented a poster paper relating to the cosmetic use of imiquimod at the 64th Annual Meeting of the American Academy of Dermatology in San Francisco. The study is described in an article entitled "Topical Imiquimod Improves Cosmetic Appearance of Photoaged Skin" published in the April 1, 2006 edition of Dermatology Times: "To Dr. Kligman's surprise, the treatment caused no local adverse reactions. However, it did result in improvements in the appearance of fine lines and wrinkles, skin texture and dyschromia that were consistent with histologic studies showing correction of epidermal dysplasia."

19. I am unaware of any publications or presentations suggesting or teaching the use of imiquimod for the treatment of normal photodamaged skin or aged skin that precede the July 28, 2003 filing date of the patent application by Drs. Baumann and Welsh.

Further Affiant says not.

Dated: February 14, 2007



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Sworn to and subscribed before
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INNOVATIVE USES OF IMIQUIMOD

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Abstract

Imiquimod (Aldara,™ 3M Pharmaceuticals) is a potent stimulator of the innate and adaptive arms of the immune system through induction, synthesis, and release of cytokines and chemokines. An extensive review of clinical trials, case reports, and letters published in peer-reviewed journals was performed regarding imiquimod use in skin disorders. A reference module was developed for physicians to consult as a guide. Studies have validated the benefit of imiquimod in treating external genital and perianal warts, superficial basal cell carcinomas, and actinic keratoses. This new topical therapeutic agent has shown to be of benefit in other various skin disorders through its broad immunomodulatory properties. Since many skin conditions are immunologically influenced, it is reasonable to expect several diseases to respond to imiquimod. Our research consolidates the therapeutic trials and reports on the innovative uses of imiquimod, thereby serving as a useful resource to benefit dermatologists treating patients with refractory or recalcitrant skin diseases.

Introduction

Imiquimod, a topically applied imidazoquinoline immunomodulator, is a potent stimulator of both the innate immune response and the cellular arm of acquired immunity. Imiquimod activates cells of the innate immune system (monocytes, macrophages, and dendritic cells) by binding to Toll-like receptor 7 on the cell surfaces. This results in the release of proinflammatory cytokines (interferon-alpha, tumour necrosis factor-alpha, interleukin-12) and chemokines (interleukins 1, 6, 8, and 10).[1] Some of the cytokines also enhance the acquired immune system, including the activation of T-helper cell type 1 and other cell-mediated immune responses that help control viruses, tumors, and intracellular parasites.[1] Even though imiquimod lacks direct antiviral or anti-proliferative activity, it has a potent indirect effect both *in vitro* and *in vivo*.

In 1997, imiquimod was approved by the FDA for the treatment of external genital and perianal warts. In 2004, it was approved for the treatment of actinic keratosis and superficial basal cell carcinoma. Beyond its established use, there are case reports and preliminary studies suggesting its effectiveness in the treatment of a wide range of malignant, infectious, and inflammatory diseases of the skin. Most of the published evidence validates the benefit of imiquimod in treating superficial basal cell carcinoma. Our intent was to explore the other off-label uses of imiquimod that have not been as extensively reviewed in the literature.

Table 1. Immunoregularity Effects of Imiquimod.

Direct effects	Indirect effects
Cytokine induction • Interferon-alpha • Interleukin 1, 6, 8, 10, 12 • Tumor necrosis factor-alpha • Interleukin 1 receptor antagonist • Granulocyte-colony stimulating factor • Granulocyte/macrophage-colony stimulating factor • Macrophage inflammatory protein 1-alpha and 1-beta • Macrophage chemotactic protein	Th-1 cytokines stimulation (including interferon-gamma) Th-2 cytokines inhibition (including interleukin-4 and 5)
B cell proliferation stimulation	
Langerhans cell activation	
Langerhans cell migration enhancement	

(Adapted with permission from: Sauder D. New immune therapies for skin disease: Imiquimod and related compounds. *Journal of Cutaneous Medicine and Surgery*. 2001; 5:S1-30).

Methods

An extensive review of clinical trials, case reports, abstracts, and review articles published in peer-reviewed journals was performed using a variety of search engines, including MEDLINE, EMBASE, Biosis, SciSearch, and International Pharmaceutical Abstracts. The findings were synthesized into chart format, creating a reference module for physicians to consult as a guide.

Dermatological diseases were classified according to their malignant, infectious, or other nature. Under these general headings, they were further subdivided and listed in alphabetical order for quick and convenient reference. The abbreviated lists of references for each disease were categorized according to article type. The highlights of the findings are summarized in the Results section.

Results

Our research reveals that imiquimod, with only three official indications (external genital/perianal warts, actinic keratosis and superficial basal cell carcinoma), has already been used as a successful treatment of over forty diseases, anecdotally or in clinical trial settings. Not all indications are listed in the tables as not to be over exhaustive. Those malignant conditions not listed include actinic cheilitis, non-superficial basal cell carcinoma (nodular, nevoid, sclerosing), Bowen's disease, bowenoid papulosis, lentigo maligna, squamous cell carcinoma, vulvar and anal intraepithelial neoplasia that seem to be accepted in dermatology practice despite not having official indication. Infectious conditions purposely omitted include common warts, flat warts, herpes simplex virus, molluscum contagiosum, papillomatosis, plantar warts, squamous papilloma, subungual/periungual warts, and verrucous papilloma.

Its potential to treat malignant conditions includes, cutaneous extramammary Paget's disease, cutaneous T-cell lymphoma, and cutaneous melanoma metastases. Infectious diseases for which imiquimod has shown promise include, leishmaniasis, epidermodysplasia verruciformis, focal epithelial hyperplasia (Heck's disease), and tinea pedis. Other effective applications of imiquimod include alopecia areata, discoid lupus erythematosus, granuloma annulare, infantile hemangioma, keloids, morphea, porokeratosis of Mibelli, silicone granuloma, squamous papilloma, stucco keratosis, UVB-induced suppression of contact hypersensitivity, verrucous papilloma, vitiligo, vulvitis circumscripta plasmacellularis, and xeroderma pigmentosum.

Table 2. Malignant Conditions.
* *[n] = number of patients*

Disease	Case Reports	Clinical trials	Reviews
Cutaneous extramammary Paget's disease	Bamford 2001 [5]* Berman 2002 [1][5] Berman 2003 [1][6] Qian 2003 [1][7] Wang 2003 [1][8] Zampogna 2002 [2][9]		
Cutaneous T-cell Lymphoma	Didona 2002 [1][10] Do 2003 [1][11] Dummer 2003 [1][12] Suchin 2002 [1][13] Wismer 2004 [1][14]	Born 2002 [17][15] Chong 2004 [4] [16] Muche 2003 [10][17]	Dummer 2002[18]
Cutaneous melanoma metastases	Bong 2002 [3][19] Hesling 2004 [1][20] Steinman 2000 [6][21] Steinman 2000 [6][22] Ugurel 2002 [1][23] Vereecken 2003 [1][24] Wolf 2003 [2][25]		

Table 3. Infectious Conditions.

Disease	Case Reports	Clinical Trials	Reviews
Fungal			
Tinea pedis		Gupta 2003 [8][26]	
Parasitic			
Leishmaniasis		Arevalo 2001 [12][27] Seeberger 2003 [12][28]	Croft 2003[29]
Viral			
Epidermo-dysplasia verruciformis	Carre* 2003 [1][30] Gisondi 2003 [1][31] Stockfleth 2000 [n/a][32]		
Focal epithelial hyperplasia (Heck's)	Maschke 2002 [1][33]		

Table 4. Miscellaneous.

Disease	Case Reports	Clinical trials	Reviews
Alopecia areata	Poochareon 2003 [3][34] D'Ovidio 2002 (**ineffective) [15][35] Sommerfeld 2001 [5][36]	Hordinsky 2003[12][37]	
Discoid lupus erythematosus	Gerdsen 2002 [1][38]		
Granuloma annulare	Kuwahara 2002 [1][39] Kuwahara 2003 [1][40]		
Infantile hemangioma	Martinez 2002 [2][41]		
Keloids		Beman 2002 [12][42]	Berman 2003[43] Poochareon 2003[44]
Morphea	Man 2003 [1][45]		
Porokeratosis of Mibelli	Agarwal 2002 [1][46] Harrison 2003 [1][47]		
Seborrheic keratosis		Mandekou-Lefaki 2004 [34][48]	
Silicone granuloma	Baumann 2003 [1][49]		
Stucco keratosis	Stockfleth 2000 [1][50]		
Vitiligo	Burkhart 1998 [n/a][51]		
Vulvitis circumscripta plasmacellularis	Ee 2003 [2][52]		
Xeroderma pigmentosum	Giannotti 2003 [1][53] Nagore 2003 [1][54] Roseeuw 2003 [2][55] Weisberg 2002 [2][56]		

Conclusions

Imiquimod has shown to be of benefit in various skin disorders as a result of its antiviral, anti-proliferative and anti-tumor activities. Since many skin conditions are immunologically influenced, it is reasonable to expect several diseases to respond to imiquimod based on its broad immunomodulatory properties. Moreover, conventional treatment modalities for various malignancies, such as Bowen's disease and lentigo maligna, often pose significant risk of scarring, deformity, and poor cosmetic appearance. Infectious conditions, such as common warts and herpes simplex virus, often pose a challenge, as they may be refractory to traditional treatment options. Accordingly, imiquimod presents an attractive new treatment option for these conditions based upon its efficacy, tolerability, convenience, and favorable cosmetic outcome.

Our research consolidates the therapeutic trials and reports on the various innovative uses of imiquimod, thereby serving as a useful resource to benefit dermatologists treating patients with refractory or recalcitrant skin diseases. Although several case reports and preliminary studies indicate the usefulness of imiquimod in the treatment of several skin conditions, in the future, rigorous controlled trials should be performed to further validate these promising reports.

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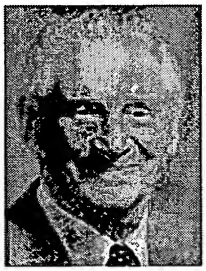
DermatologyTimes
The Leading Newsmagazine for Dermatologists

Topical imiquimod improves cosmetic appearance of photoaged skin

Histology shows repair of photodamage

Aug 1, 2006
By: Cheryl Guttman
Dermatology Times


Dr. Kligman

National report — Recent studies conducted with the topical immune response modifier imiquimod 5 percent cream (Aldara, 3M Pharmaceuticals) suggest cosmetic improvement of photoaged skin may be another one of its benefits.

Albert M. Kligman, M.D., Ph.D., and Raymond L. Cornelison, Jr., M.D., and colleagues at Oklahoma University Health Science Center report clinical and histological evidence demonstrating anti-aging effects associated with imiquimod treatment.


Dr. Cornelison

Improvement in the appearance of photoaged skin turned out to be a serendipitous finding of a study Dr. Kligman had undertaken to investigate if imiquimod could be used as field therapy to reveal and treat subclinical actinic keratoses (AKs) in persons with moderate facial photodamage but no clinically apparent AKs. He enrolled 10 white women who were instructed to apply imiquimod once daily on five consecutive days of the week for four weeks.

To Dr. Kligman's surprise, the treatment caused no local adverse reactions. However, it did result in improvements in the appearance of fine lines and wrinkles, skin texture and dyschromia that were consistent with histologic studies showing correction of epidermal dysplasia. No dermal changes were observed.

Cosmetic effect

"The cosmetic effects of this treatment were quite remarkable and the patients were very pleased with the results.

"Currently, imiquimod is a valuable medication for the treatment of precancerous and cancerous skin lesions. The results of this study suggest it has interesting potential for cosmetic use as well," says Dr. Kligman, professor of dermatology, University of Pennsylvania, Philadelphia.

Study specifics

The women participating in the study ranged in age from 33 to 55 years old and were fair-skinned (Fitzpatrick phototypes I or II).

Evaluations of clinical responses to the treatment included subjective and objective measures. Assessments of global improvement in skin appearance by the investigator showed nine (90 percent) of the 10 women benefited with slight or moderate improvement in global appearance, while nine (90 percent) subjects rated the improvement as moderate to great.

In addition, five women selected for having the greatest severity of photodamage underwent additional studies, including hydration assessment with measurement of skin capacitance and hygroscopicity, chromametric assessment and punch biopsies. The hydration studies showed no changes in skin capacitance or water desorption rate constant. Hygroscopicity and water holding capacity improved, but the changes from baseline were not statistically significant.

"These studies indicate that the hydration level below the skin surface was not affected by the treatment, but that there was increased water content in the superficial, desquamating portion of the stratum corneum," Dr. Kligman says.

Study results

The colorimetry studies showed a decrease in mean reflectance indicative of reduced scaling and corresponding to the women's reports of improved surface smoothness.

Histology revealed elimination of epidermal thickening and keratinocyte atypia accompanied by reduced epidermal melanin content and more uniform melanin distribution, which Dr. Kligman notes is consistent with observations of reduced clinical mottling.

Dr. Cornelison and colleagues report similar epidermal histologic changes — but also note effects on the dermis — in their study that evaluated tissue specimens obtained from patients enrolled in a clinical study of imiquimod treatment for lentigo maligna (LM). The subjects in that trial applied imiquimod daily for three months and had pre-and post-treatment biopsies performed to assess LM clearance.

Specimens were available from 26 subjects, and 24 (92 percent) of those patients were determined to be complete responders in terms of LM disappearance. However, semiquantitative grading of a variety of histologic parameters also showed restoration of normal epidermal thickness and melanization as well as significant increased papillary dermal fibroplasia and significantly decreased solar elastosis in 24 patients (92 percent).

"While photoaging is generally considered primarily a cosmetic problem, the fact that it constitutes the background for the development of precancerous and cancerous skin lesions highlights its importance as a medically significant problem. Further studies are needed to see if the positive changes observed in this trial are also seen in photoaged skin not associated with LM," says Dr. Cornelison, professor and chair, department of dermatology, Oklahoma University Health Science Center, Oklahoma City.

Both investigators also note more research is needed to understand the mechanisms mediating the effects of imiquimod treatment on photoaged skin.

"It is known that imiquimod interacts with toll-like receptor 7 to induce transcription of a variety of pro-inflammatory genes. Whether that pathway or another mechanism underlies the reparative effects observed is unclear," Dr. Cornelison says.

Disclosure: Neither Dr. Kligman nor Dr. Cornelison report any financial interest in 3M or imiquimod.